REMARKS and RESPONSE TO RESTRICTION REQUIREMENT

In this second Restriction Requirement, the examiner has reiterated his previous assertion that the claims are directed to more than one invention and that the inventions are not linked so as to form a single general inventive concept under PCT Rule 13.1. The claims again have been divided as follows:

Group I: claims 22-33 and 37-38, directed to a recombinant Fel d 1 fusion product;

Group II: claims 34-36 and 40-41, directed to DNA sequences encoding a recombinant Fel d 1 fusion product;

Group III: claim 39, directed to a method for diagnosing cat allergy.

The examiner asserted that the inventions listed as Groups I - III do not relate to a single general inventive concept under PCT Rule 13.1 because, under Rule 13.2, they lack the same or corresponding special technical features. Specifically, the invention of Group I was found to have no special technical feature that defines the contribution over the prior art of Vailes et al, *J. Allergy Clin. Immunol.* 110 (5):757-762 (2002) in view of George et al., *Protein Engineering* 15(11):871-879. The Vailes reference was described as teaching a recombinant Fel d 1

fusion product comprising a Fel d 1 chain 1 and a Fel d 1 chain 2, wherein the N-terminal amino acid of chain 2 is linked to the C-terminal amino acid of chain 1 through a 19 amino acid linker.

The examiner acknowledged that the claimed invention differs from the Vailes reference in the recitation of "a peptide linker consisting of 1 to 9 amino acid residues." She asserted, however, that the George et al. paper teaches that small and medium oliogonucleotide linkers consisting of 1 to 14 amino acids can be used to link chimeric proteins and specifically teaches many particular linkers of nine or fewer amino acids, particularly many dyad linkers. She asserted that it would have been obvious to substitute a 1 to 9 amino acid linker in the recombinant Fel d 1 fusion product comprising a Fel d 1 chain 1 and a Fel d 1 chain 2 wherein the N terminal amino acid of chain 2 is linked to the C-terminal residue of chain 1 by way of a 19 amino acid linker because the George et al. paper teaches that linker length can be optimized for function and the prevention of unfavorable interactions between the protein domains being linked. She further asserted that it would have been obvious to determine the optimal linker length to link the recombinant Fel d 1 fusion product of Vailes et al. and that George et al. teach that many dyad linkers are useful in chimeric proteins.

The priority date of the present application is April 23, 2003. The Vailes paper and the George paper were published less than one year before the priority date of the present application.

Attached hereto as Exhibits A1 and A2 are, respectively, a copy of the Vailes et al. paper, with a date stamp from the Library of Congress which shows that the issue of the journal in which this paper appeared was received by the Library on November 27, 2002, and a copy of the same paper as printed from an on-line source which shows that the paper was available on-line as of January 7, 2003. Attached hereto as Exhibit B1 is a copy of an e-mail sent from an assistant production editor of the Oxford Journals, Oxford University Press, which advises that the issue of the journal in which the George et al. paper appeared was sent to subscribers on January 23, 2003.

Enclosed herewith is a Declaration Pursuant to 37 C.F.R. § 1.131, signed by inventor Hans Grönlund. An unsigned copy of the declaration is being submitted; a copy of the executed declaration will be submitted shortly. Attached to the declaration are photocopies of laboratory notebook pages from one of Dr. Grönlund's laboratory notebooks. The photocopies are true and exact copies of the original notebook pages with the exception that the dates of the experiments have been redacted.

All of the experimental work recorded, however, took place well before November 27, 2002, and so preceded the earliest publication date of either the publications cited by the examiner. The laboratory notebook pages reflect the reduction to practice of the present invention. More specifically, the pages show the assembly by PCR of Fel d 1 chain 1; the assembly by PCR of Fel d 1 chain 2; the expression and purification of the two chains; a discussion of cat allergic patients and ELISA RAST of the two chains separately; assembly of Fel d 1 construct (2+1) (i.e., the 3' end of the chain 2 sequence linked to the 5' end of the chain 1 sequence) and Fel d 1 construct (1+2) (i.e., the 3' end of the chain 1 sequence linked to the 5' end of the chain 2 sequence) by PCR; ligation of the two fragments into a vector, transformation and sequencing; ligation of the Fel d 1 (2+1) and (1+2) constructs into expression strain BL21PLysS; and expression of the (2+1) and (1+2) by SDS PAGE.

Also submitted with the laboratory notebook pages are copies of the order sheets for the primers used in the constructions. Again, these papers are accurate reproductions of the original order sheets with the exception that the dates on the original order sheets have been redacted. The original order sheets, however, were made well before November 27, 2002.

These pages show reduction to practice of the present invention prior to the publication dates of the Vailes et al. and George et al. references. Neither reference, therefore, is prior art against the claims of the present application.

For the record, Applicants also take issue with the examiner's assertion that the teachings of the George reference when combined with the teachings of the Vailes reference, are sufficient to render the present invention obvious, such that the claims of this application lack a special technical feature over the teachings of the references. Vailes et al. were seeking to engineer a recombinant Fel d 1 with antibody binding "comparable to that of the natural allergen." They further noted (second paragraph, second column of first page of the article) that "production of recombinant (r) Fel d 1 has been challenging...." Vailes et al. then report on the preparation of a recombinant Fel d 1 having a 19 amino acid linker. One of skill in the art reading Vailes would come away with the clear understanding that a recombinant Fel d 1 is a challenging fusion product to prepare and that a lengthy linker is required to mimic the natural protein.

Turning to the George reference, Applicants respectfully submit that the examiner misinterpreted Tables II - VII. These tables are not teaching the skilled person to use amino acid

pairs as the linker; rather they are investigating the propensity of amino acid pairs within longer linkers. Page 875, first column, first sentence under the heading "Dipeptide propensities for linkers," explains that the authors are considering "dipeptide propensities for all linkers and medium sized linkers." The headings in Tables III and IV make it clear that the authors are considering "all linkers" and "medium sized linkers," respectively - not dipeptides. Tables V and VI relate to "non-helical" and "helical" linkers, again suggesting longer linkers.

George et al. then provide a rather general conclusion in the final two columns. The reference certainly does not teach the use of shorter linkers. If anything, one of skill in the art would be taught that he should seek to investigate the structure of the 19 amino acid linker in Vailes et al. with a view to introducing more tailored diads. It also is important to note that George et al. are not concerned with specific problems concerning mimicking of the properties of naturally occurring Fel d 1. George et al. therefore provide no more than suggestions for a lengthy research project into the nature of the linker in Vailes et al. The authors provide only suggestions for a lengthy research project into the nature of the linker used by Vailes et al. They certainly do not give one of skill in the art any

expectation that one could reduce sensitization in a patient while simultaneously maintaining the immunological properties of the protein by providing a bond or a 1-9 amino acid linker.

Applicant thus respectfully requests that the restriction requirement be withdrawn.

Applicant recognizes that, although he believes that the restriction requirement should be withdrawn, he is under an obligation to elect one of the groups of claims in the event that the examiner makes the restriction requirement final. Accordingly, Applicant hereby elects the claims of Group I. Applicant requests, however, that in view of the discussion and set forth above and accompanying evidence, all of the pending claims should be examined together.

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